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(71) Applicant *(for all designated States except BB US)*: DUSTIN INVESTMENTS CC [ZA/ZA]; c/o Kessel Feinstein, 4th floor, 14 Long Street, Cape Town, 8001 (ZA).

(71) Applicant *(for BB only)*: HANDELMAN, Joseph, H. [US/US]; 26 West 61st Street, New York, NY 10023 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BUTLION, Michelle [ZA/ZA]; 204 Argonaut, Hall Road, Cape Town, 8001 (ZA).

(74) Agents: HANDELMAN, Joseph, H.; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US) et al.

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(54) Title: A COMPOSITION FOR USE AS A PHARMACEUTICAL AND IN SPECIFIC AGRICULTURAL AND INDUSTRIAL APPLICATIONS

(57) Abstract

The present invention provides a composition for use as an antimicrobial agent comprising the active ingredients: a quaternary ammonium compound and a guanidinium component. The composition has application in pharmaceutical, cosmetic, food, leather tanning and agricultural industries.

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A COMPOSITION FOR USE AS A PHARMACEUTICAL AND IN SPECIFIC AGRICULTURAL AND INDUSTRIAL APPLICATIONS

THIS INVENTION relates to a composition for use as a pharmaceutical and in specific agricultural and industrial applications.

In this specification, the term "animal body" should be understood to include an egg.

For purposes of this specification, the term "the relevant fields of application" should be understood to mean, exclusively, the fields of agriculture, horticulture, floriculture, leather manufacture or processing, tobacco and fur processing, paint-, cosmetics-, rope-, plastics-, fuel-, oil- and rubber manufacture, brewing, canning, bottling, water storage and supply (including swimming pool care), and shipping (specifically, treatment of ballast water of ships or other waterborne vessels).

According to one aspect of the invention, there is provided a substance or composition for use in a method of treatment of a human or animal body by therapy, the substance or composition including in combination as active ingredients,

a guanidine component; and

at least one quaternary ammonium compound (hereinafter referred to as a "QAC");

said method comprising administering an effective amount of said substance or composition to said human or animal body.

The treatment by therapy may be treatment of diseases or infections arising from pathogens such as viruses, bacteria, mycobacteria, mycoplasma and fungi.

The pathogens may be selected from the group consisting of Feline Herpes virus, HIV virus, Polio virus, Influenza virus, Feline Calicivirus, Canine Parvovirus, Newcastle Disease virus, Infectious Bursal Disease virus, Infectious Laryngotracheitis virus, Infectious Bronchitis virus, Pox virus, Bacteriophages, *Pseudomonas auriginosa, Escherichia coli, Acinetobacter anitratus, Klebsiella pneumonia, Bacillus subtilis* spores, *Bacillus subtilis* vegetative, *Bordetella* spp., *Salmonella* spp., *Shigella sonnei, Staphylococcus aureus, Streptococcus faecium, Vibrio* spp., *Lactobacillus fermentum, Micrococcus luteus, Corynebacterium* spp., *Proteus vulgaris, Klebsiella pneumoniae, Clostridium* spp., *Ornithobacterium rhinotrachaele, Haemophilus paragallinarum, Pasteurella gallinarum, Mycoplasma* spp., *Mycobacterium tuberculosis, Mycobacterium leprae, Aspergillus* spp., *Candida albicans*, and *Trichophyton mentagrophytes*.

According to a further aspect of the invention there is provided use, in the manufacture of a medicament to treat, control or prevent diseases or infections of the human or animal body caused by pathogens, of a composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC.

The pathogens may be selected from the group as hereinbefore described.

According to a further aspect of the invention there is provided a method of treatment or prophylaxis of diseases or infections of a human or animal body caused by pathogens, the method including the steps of administering to an afflicted human or animal body a composition which includes, in combination as active ingredients,

a guanidine component; and

at least one QAC.

The pathogens may be selected from the group as hereinbefore described.

The invention extends, in a further aspect, to a composition for use as a prophylactic in the control or prevention of diseases or infections of the human or animal body caused by pathogens, the composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC.

The pathogens may be selected from the group as hereinbefore described.

The prophylactic use may include applying the composition by a mode selected from spraying, dipping, fogging and injecting of the human or animal body with the composition, dissolved in a suitable carrier such as water, thereby to serve as a disinfectant and to provide biosecurity of the human or animal body. The animal body may be a body of an animal selected from chickens, pigs and horses. The treatment may be spraying of the animal body.

The animal body may be an egg and the application mode may be selected from spraying and injecting.

Thus, the composition may be applied prophylactically to poultry eggs, either externally, e.g. by spraying, or internally by injecting into the egg, as a means of reducing contamination by pathogens (e.g. contamination by mycoplasma).

The composition may be applied at a concentration in a range of from 1 part per million to 500 000 parts per million of the combined active ingredients in a solvent e.g. water. Preferably, it is applied at a concentration in

a range of from 1 part per million to 10 000 parts per million of the combined active ingredients in water.

The prophylactic use may include the use of the composition as a disinfectant for all types of surfaces which need to be kept free of said pathogens so as to control or prevent diseases or infections associated with said pathogens. This would include, for example, the use of the composition for disinfection of animal feed, animal carcasses and animal dip-tanks.

The prophylactic use may include use of the composition as a water disinfectant for controlling or preventing disease caused by water-borne pathogens. The prophylactic use may include use of the composition as an air disinfectant effective in controlling or preventing disease caused by air-borne pathogens.

Thus, the invention extends, in a further aspect, to a disinfectant composition which includes, in combination as active ingredients,

a guanidine component; and

at least one QAC.

The invention also provides a pharmaceutical composition for use in treatment or prophylaxis of diseases or infections of a human or animal body caused by pathogens, the pharmaceutical composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC;

the pharmaceutical composition further including at least one ingredient selected from the group consisting of carriers, excipients, diluents and adjuvants.

The pathogens may be selected from the group as hereinbefore described.

The pharmaceutical composition may be in a form suitable for oral, rectal, intravaginal, topical, or parenteral administration.

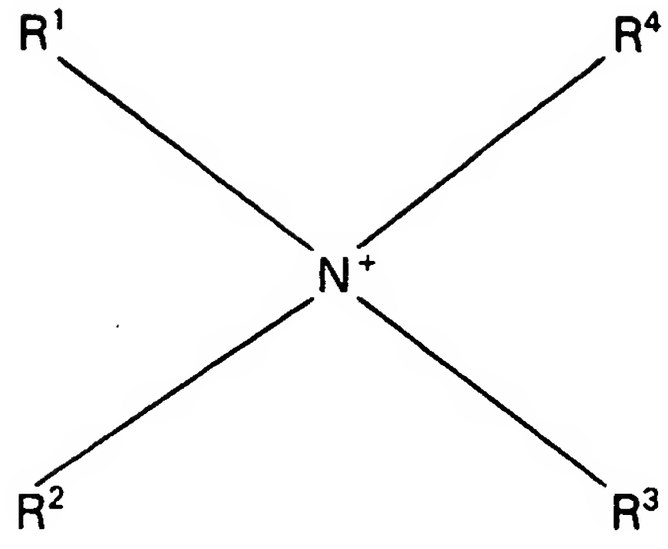
Typically, the pharmaceutical composition is in unit dosage form and each unit dosage preferably contains from 0,1 to 1000 mg of the active ingredients, advantageously from 1 to 500 mg thereof.

When in a form suitable for solid oral, rectal or intravaginal administration, the pharmaceutical composition may include conventional solid preparation carriers such as gelatin, lactose and starch. When in a form suitable for liquid oral administration, the composition may include conventional liquid carriers and diluents such as suspending, emulsifying, stabilizing, preserving, sweetening, flavouring or colouring agents.

The pharmaceutical composition may be a topical composition in a form suitable for topical application, internally or externally. The topical composition may thus be in a form such as a liquid spray, powder, nasal drops or a throat paint. The topical composition may be prepared in oily, aqueous or powdered media for application in the form of a paint, lotion, cream, ointment, aerosol or dusting powder.

When in a form suitable for parenteral administration, the pharmaceutical composition may comprise an aqueous or an oily solution.

In all of the aforegoing aspects of the invention the QAC may be represented by the general formula (I)



.....(I)

wherein:

at least one of R_1, R_2, R_3 and R_4 is an acyclic group having 6 to 24 carbon atoms;

when any two of R_1, R_2, R_3 and R_4 each is an acyclic group having 6 to 24 carbon atoms, then the remainder of R_1, R_2, R_3 and R_4 are each independently selected from alkyl and hydroxyalkyl groups having from 1 to 4 carbon atoms, and a benzyl group; and may together with the nitrogen atom form a piperidinyl or morpholinyl group; and

X^- is chloride or any other pharmaceutically acceptable anion.

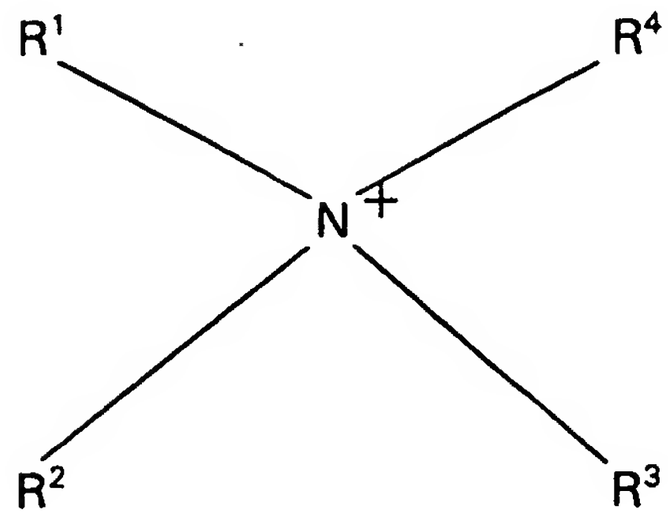
The acyclic group having 6 to 24 carbon atoms may be a substituted aliphatic group of which the substituent may be an ether group.

The acyclic group or groups preferably have from 8 to 14 carbon atoms.

As indicated above, a single QAC may be used. However, a combination of the defined QAC's may also be used.

The QAC may be didecyl-dimethyl ammonium chloride, cetyl-trimethylammonium chloride, alkyl-benzyl-dimethylammonium chloride or any other QAC wherein the acyclic group or groups are similar to those of naturally occurring substances such as coconut acid or cetyl-dimethyl-ethyl ammonium ethyl sulphate.

The QAC may have a general formula (IA)



.....(IA)

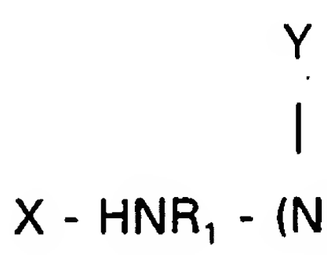
wherein:

R^1 and R^4 are the same or different and each is independently selected from the group consisting of C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{20} aryl, C_4-C_{20} alkaryl, C_4-C_{20} aralkyl and C_5-C_{20} alkaralkyl;

R^2 and R^3 are the same or different and each is independently C_1-C_6 alkyl; and

X^- is an anion.

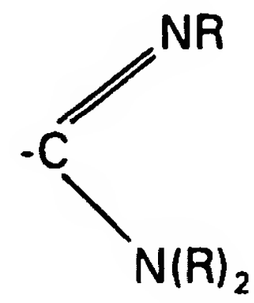
The guanidine component may include guanidine compounds having a general formula (II)



$$X - HNR_1 - (NR_2)_n - NH - X \quad \text{.....} \quad (II)$$

wherein:

X and Y are each hydrogen or a carboxamidine group having a general formula (III)



.....(III)

wherein R is H or an alkyl group having 1-4 carbon atoms, with the proviso that at least one of X and Y must be a carboxamidine group of formula (III) as defined above;

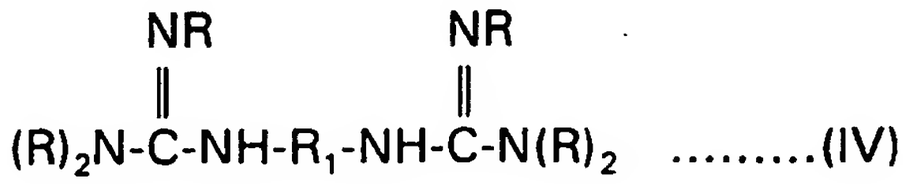
R_1 and R_2 are alike or independently different aliphatic groups selected from groups having 3-14 carbon atoms, preferably alkyl groups having 6-12 carbon atoms including those selected from the group consisting of hexyl, heptyl, octyl, nonyl, decyl, and dodecyl, most preferably alkyl groups having 6-9 carbon atoms; or cycloalkyl groups selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and

n is 0 to 6, preferably 0 to 4; provided that for values of $n > 1$, R_2 may differ for each value of n.

The guanidine component may include at least one of a guanidinised aliphatic diamine, a guanidinised aliphatic polyamine, or a mixture of a guanidinised aliphatic diamine and a guanidinised aliphatic polyamine.

The guanidine component may include guanidinised amines present as acid addition salts. Thus, the guanidinised amines may be present as acid addition salts selected from the group consisting of chlorides, sulfates, nitrates, acetates, formeates, stearates and oleates.

The guanidine component may include a guanidinised aliphatic diamine having a general formula (IV)



$$(R)_2N\text{-}C(=NR)\text{-}NH\text{-}R_1\text{-}NH\text{-}C(=NR)\text{-}N(R)_2 \quad \text{.....(IV)}$$

wherein:

R is as defined above; and

R_1 is an alkyl group having 3-14 carbon atoms, preferably 6-12 carbon atoms.

The guanidine component may include a guanidinised aliphatic polyamine having a general formula (V)

$$X\text{-}HNR_1\text{-}(\underset{\substack{|\\ Y}}{N}R_2)_n\text{-}NH\text{-}X \quad \text{..........(V)}$$

wherein:

X and Y are as defined above;

R_1 and R_2 are independently aliphatic groups having 3-14 carbon atoms, preferably 6-12 carbon atoms; and

n is 1 to 6, preferably 1-4; provided that, for values of $n > 1$, R_2 may differ for each value of n.

The guanidinised aliphatic polyamine may have a general formula (VI)

$$X\text{-}HNR_1\text{-}NHR_2\text{-}NH\text{-}X \text{ .... (VI)}$$

wherein X, R_1 and R_2 are as defined above.

The guanidine component may include 0-100% diamine, 0-100% triamine and 0-60% tetramine and higher polyamines, on a mass basis. Preferably, the guanidine component includes 0-40% diamine, 60-100% triamine and 0-30% tetramine and higher polyamines, on a mass basis. Such a guanidine component may have a guanidinising grade in excess of 45%, preferably in excess of 70%, and most preferably between 70% and 95%.

When the guanidine component comprises guanidinised aliphatic polyamines, it may include a mixture of polyamines of general formula (V) with

a guanidinising grade exceeding 30%. Preferably the guanidinising grade exceeds 70%. By guanidinising grade is meant the ratio, expressed as a percentage, of the total number of carboxamidine groups in the mixture of polyamines, to the total number of N atoms in the mixture.

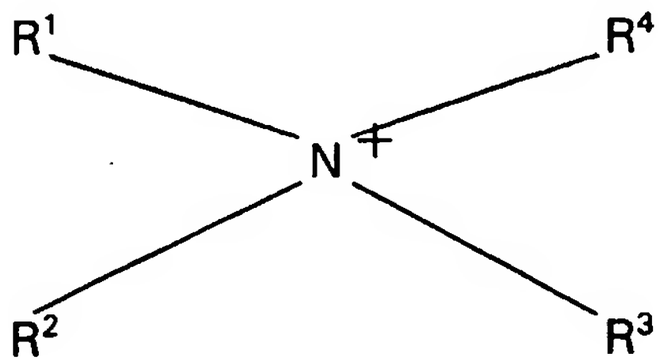
The most preferred polyamines of general formula (V) have aliphatic groups (substituents R_1 and R_2) having 8 carbon atoms.

The guanidine component may be produced by guanidinising mixtures of technical grade amines with cyanamide, urea or thiourea derivatives up to the desired guanidinising grade.

According to a further aspect of the invention, there is provided an antimicrobial composition for use in the relevant fields of application as herein defined, the composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC having the general formula (IA) as hereinbefore set out



.....(IA)

wherein:

R^1 and R^4 are the same or different and each is independently selected from the group consisting of C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{20} aryl, C_4-C_{20} alkaryl, C_4-C_{20} aralkyl and C_5-C_{20} alkaralkyl;

R^2 and R^3 are the same or different and each is independently C_1-C_6 alkyl; and

X^- is an anion.

The alkyl and alkenyl moieties of the substituents R_1, R_2, R_3 and R_4 of the QAC are suitably either straight-chain or branched-chain in configuration.

Preferably, R_2 and R_3 are both methyl.

Preferably, although not necessarily, the total number of carbon atoms in the moieties of the substituents R_1 and R_4 does not exceed 30, to facilitate solubility of the QAC in water.

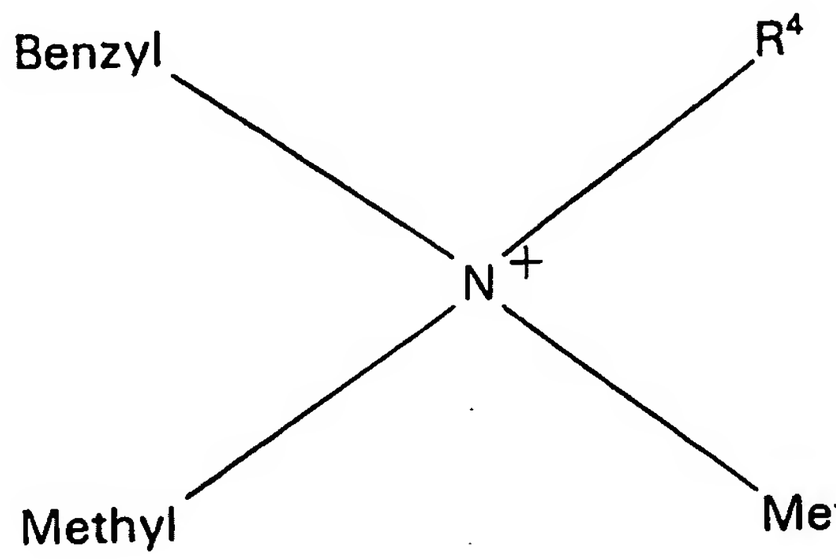
The QAC may be derived from naturally-occurring fatty acids, such as coconut oil, tallow, hydrogenated tallow, palm oil and the like. Thus, a combination of different QAC's of formula (IA) as defined may be used, i.e. the antimicrobial composition may include mixture of different specific compounds falling within the definition of formula (IA), in which the alkyl and/or alkenyl moieties correspond to those in the fatty acid precursors.

The antimicrobial composition may further contain minor quantities of QAC's similar to those hereinbefore defined, but differing in that the corresponding alkyl and/or alkenyl moieties are of lower or higher molecular weight than those specified in formula (IA). QAC's of this type may result when the QAC component of the formulation is derived from a naturally occurring material.

The alkyl and/or alkenyl moieties of the QAC of formula (IA) may be capric, lauric, myristic, palmitic, stearic, dodecyl, decylenic, dodecylenic, palmitoleic, oleic, ricinoleic, linolenic, petro-selenic, linoleic, eleostearic, and the like.

As indicated in the definitions for the substituents R^1 and R^4, these groups may contain a phenyl group, which is linked to the nitrogen atom by an alkylene moiety, and/or is substituted by alkyl. The anion X^- may be an anion of a suitable organic or inorganic acid. Preferably, the anion X^- is selected from the group consisting of chloride and bromide.

The QAC may have a general formula (VII)



.....(VII)

wherein R^4 is alkyl or alkenyl of from 8 to 18, preferably 12 to 18, carbon atoms and "Hal^-" is a chloride or bromide anion.

Non-limiting examples of QAC's useful as active ingredients in the antimicrobial compositions in accordance with the invention include the following: alkyl dimethyl benzyl ammonium chlorides, dimethyl di(hydrogenated tallow) ammonium chloride, trimethyl tallow ammonium chloride, dimethyl dicoco

ammonium chloride, dioctyl dimethyl ammonium chloride, didecyl dimethyl ammonium chloride, alkyl dimethyl ethyl ammonium bromide, cetyl trimethyl ammonium bromide, alkyl dimethyl ethylbenzyl ammonium chloride, tetradecyl dimethyl benzyl ammonium chloride mono-hydrate, myristyl dimethyl benzyl ammonium chloride, stearyl dimethyl benzyl ammonium chloride, myristyl trimethyl ammonium chloride, trimethyl palmitic ammonium chloride, trimethyl tallow ammonium chloride, myristyl dimethyl benzyl ammonium chloride dihydrate, hydrogenated tallow dimethyl benzyl ammonium chloride, alkyl dimethyl benzyl ammonium bromide, alkyl trimethyl ammonium bromide, dialkyl dimethyl ammonium chloride, benzyl dimethyl hexadecyl ammonium chloride, coco trimethyl ammonium chloride, and dodecylbenzyl trimethyl ammonium chloride.

The guanidine component may include guanidine compounds as hereinbefore described.

The antimicrobial compositions in accordance with the invention may include the QAC and the guanidine component in a mass ratio range of 1:1-20:1. Preferably, the mass ratio range is 2:1-10:1.

The compositions may be produced by mixing the QAC and the guanidine component in aqueous solution.

The use of the antimicrobial composition may be inhibition of microbial growth wherever such microbial growth is undesirable in the relevant fields of application. The microbial growth may be a growth of microbes such as fungi (including yeasts), bacteria, malts, algae and viruses.

In particular, the use of the antimicrobial composition in agriculture, horticulture and floriculture may be inhibition of the growth of microbes present on growing crops and/or harvested produce obtained therefrom. The use of the antimicrobial composition in leather tanning, tobacco and fur processing, paint-,

cosmetics-, rope-, plastics-, fuel-, oil- and rubber- manufacture, brewing, canning, bottling, water storage and supply, and shipping may be inhibition of microbes growing in aqueous systems employed in these fields.

For purposes of interpretation of the present specification, the terms "antimicrobial" and "inhibition of microbial growth", and associated derived terms, have meanings which include the killing or destruction of, as well as the inhibition, or control of, growth and/or propagation of fungi (including yeasts), bacteria, malts, algae and viruses in dormant, immature, developing and/or mature stages of development. Thus, also, the term "microbes" should be understood to accommodate fungi (including yeasts), bacteria, malts, algae and viruses in the aforementioned stages of development, unless otherwise indicated.

Non-limiting examples of microbes, the growth of which in the relevant fields of application may be inhibited by the antimicrobial composition, are

Fusarium culmorum, Septoria nodorum, Fusarium nivale, Fusarium oxysporum, Podosphaera leucotricha, Phytophthora infestans, Oidium tuckeri, Xanthomonas campestris, Plasmopara viticola, Pseudoperonospora cubensis, Botrytis cinerea, Sphaerotheca fulignea, Pseudomonas syringae, Alternaria solani, Peronospora destructor, Phomopsis citri, Colletotrichum dematium, Penicillium italicum, Mycosphaerella musicola, Sclerotinia fructigena, Fusarium roseum, Phoma exigua, Rhizopus spp., *Trichoderma* spp., *Xanthomonas oryzae, Pseudomonas aeruginosa, Erwinia carotovora, Escherichia coli, Aspergillus* spp., *Staphylococcus aureus, Micrococcus* spp., *Chlorella* spp., *Klebsiella* spp., and *Candida* spp.

Use of the antimicrobial composition in agriculture, horticulture and floriculture may be to combat microbes present on, and which may cause damage to and/or disease of, growing crops, plants, trees, seeds, flowers, fruits and vegetables. The use of the antimicrobial composition in agriculture may instead or in addition be to combat such microbes present on harvested produce

(excluding harvested timber). The use of the antimicrobial composition in agriculture may instead or in addition be to combat such microbes found on equipment and implement surfaces, packing shed surfaces, and other general agricultural surfaces. The use of the antimicrobial composition may be use to combat microbes present on or in soils to be used for agricultural purposes.

The term "seeds" is intended to indicate generally propagative plant matter, and therefore includes for example, cut stems, corms, bulbs, rhizomes and the like.

Moreover, the term "harvested produce" includes harvested forage crops, such as barley, oats, rice, sorghum, maize; forage crops that are suited for ensiling, such as grass, maize, clover, lucerne, beans, peas, bore cole and sugar beets; and cut flowers.

The antimicrobial composition may be applied to crops, etc. and harvested produce already infested with, or liable to infestation with, microbes, especially fungi and bacteria.

The use of the antimicrobial composition in agriculture may be use as a disinfectant of surfaces which need to be kept generally free of microbes likely to affect crops, etc. and harvested produce, so as to limit or prevent associated diseases.

The use of the antimicrobial composition in agriculture may thus include use of the composition for disinfection of irrigation water, fruit and vegetable dip-tank water and other water used in agriculture which could transmit damage or disease to crops, etc. and/or harvested produce, due to waterborne fungi or bacteria.

The use of the antimicrobial composition in agriculture may also include use of the composition for the treatment of irrigation water to prevent or

inhibit blockages and/or slime build-up in an irrigation system caused by microbes such as algae, fungi and bacteria.

The use of the antimicrobial composition in agriculture may include use of the composition as an air-disinfectant effective against airborne fungi and bacteria potentially harmful to crops, etc.

The use of the antimicrobial composition may be to combat microbes capable of causing degradation and deterioration of industrial products such as leather, and aqueous systems associated with products such as adhesives, resins, beverages, food, drilling fluids, pigment dispersions, latex paints and oleoresinous coatings.

The use of the antimicrobial composition may be inhibition of microbial growth in evaporative condensers, heat exchange water towers, influent systems such as flow-through filters and industrial scrubbers. These systems suffer reduction in efficacy due to high microbial load, which may be controlled by the use of the antimicrobial composition.

Thus, the formation of slime by microorganisms in the water from cooling towers may be impeded by use of the antimicrobial composition, thus limiting deterioration, corrosion, fouling and decreased efficacy of the cooling tower which might otherwise result.

The use of the antimicrobial composition may be as a disinfectant of ballast water of a ship or other water-borne vessel, before the water is discharged to sea or other body of water on which said ship or vessel travels.

The use of the antimicrobial composition may be as a disinfectant of bottles and other containers employed or treated in breweries, canning and/or bottling plants.

The use of the antimicrobial composition may be as a disinfectant of pools, ponds, lagoons, lakes and other reservoirs of water.

The use of the antimicrobial composition may involve contacting the composition with microbes, the growth of which is to be inhibited. This may be accomplished by continuous dosing, by application of the composition as a combined, single composition, including the guanidine component and the QAC or QAC's, or by application of the guanidine component and QAC or QAC's separately.

Such separate administration of the guanidine component and QAC or QAC's may be either at the same time or at different times. The result in either case is similar: the article or system being treated with the composition will ultimately have incorporated therein or have applied thereto a desired dosage concentration of each component.

In the treatment of aqueous systems, such as cooling systems employing water, or pools, ponds, lagoons or lakes, to inhibit the growth and/or propagation of microbes, the antimicrobial composition may be introduced as a single system including the two active ingredients, at one or at multiple points in the system. Alternatively, the active ingredients may be introduced separately, at the same or at different points and or times of introduction, provided that the active ingredients eventually combine to form the composition of the invention.

The antimicrobial composition may be used in diverse formulations. Thus, the composition may be applied as a solid (e.g. divided powders or granular materials) or as a liquid (e.g. as a solution, dispersion, emulsion, suspension, concentrate, emulsifiable concentrate, slurry, or the like), depending upon the application intended, and the formulation medium desired. The solution, dispersion, or emulsion may be prepared by dissolving the active ingredients in an organic or aqueous solution which may contain at least one wetting agent, dispersive agent or emulsifier.

The antimicrobial composition may also be applied as an aerosol. Thus, the composition may be kept under pressure in a container with a propelling gas, such as fluortrichlormethane or dichlordifluormethane.

Where the antimicrobial composition is to be used in the form of an aqueous dispersion or emulsion, the composition may be supplied in the form of a concentrate, containing a high proportion of the active ingredients. The concentrate may be diluted with water before use.

The concentrate of the antimicrobial composition may contain from 4-85% and typically from 4-50% by weight of the combined active ingredients. A 10-20% aqueous solution is generally preferred as a concentrate. The concentrate may contain conventional excipients such as dispersants, stabilisers, preservatives, co-solvents, diluents, and the like.

The antimicrobial composition may be applied to surfaces in the agricultural, horticultural and floricultural fields by application methods familiar in these fields. For example, the composition may be applied as a solid substance, fluid substance, solution, dispersion, or emulsion. The composition may contain, in addition to the guanidine component and the QAC, at least one aid such as an insecticide, fungicide, bactericide, algaecide or other biologically active substance. Such an aid may, for example, be used to extend the range of diseases which may be combatted by the composition. The antimicrobial composition may, furthermore, include at least one wetter, buffer or sticker.

The antimicrobial composition in its prepared form may, for example, be applied by spraying (including spraying with atomisers) the prepared composition onto surfaces to be treated. Further non-limiting examples of methods of applying the composition to the surfaces include plunging, dipping or soaking articles to be treated in the composition.

The antimicrobial composition may be formulated with a variety of diluents or carriers suitable in the relevant fields of application. Typical diluents or carriers include, for example, kaolin, bentonite, silicone, dolomite, calcium carbonate, talc, powdered magnesia, gypsum, Hewitt's earth, and China clay. Preparations of the composition for the dressing of seed may, for example, contain an agent that enhances the adhesion of the composition to the seed, for example, a mineral oil.

The antimicrobial composition has activity against microbes when employed at levels of concentration appropriate for each of the relevant fields of application. The required effective concentration may vary for particular microbes and in particular applications. In general, however, the composition may be applied at a concentration of from 1 part per million to 500 000 parts per million of the combined active ingredients in e.g. water. Preferably, the composition is applied at a concentration of 1 part per million to 10 000 parts per million of the combined active ingredients in e.g. water.

The antimicrobial composition of the invention has a synergistic activity not explained merely by addition of the individual effects of the active ingredients.

Although the synergistic activity exhibited by the two active ingredients when in combination as the antimicrobial composition may be due to their presence as discrete chemical entities, chemical interactions between the two active ingredients and the formation of adducts or cross-reaction products is possible. Such additional active species, for use in the relevant fields of application, are also encompassed within the scope of the present invention.

According to a further aspect of the invention there is provided a method of inhibiting growth of microbes in the relevant fields of application as herein defined, which includes the step of contacting said microbes with a

microbicidally effective amount of the antimicrobial composition as hereinbefore described.

In accordance with yet another aspect of the invention there is provided a substance or composition for use in a method of treatment of a human or animal body by therapy, and for use in the relevant fields of application as herein defined, the composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC;

said method of treatment comprising administering an effective amount of said substance or composition to said human or animal body;

provided that the guanidine component is not imine octadine triacetate.

The QAC, the guanidine component and the use in the relevant fields of application may be as hereinbefore described.

Further according to the invention there is provided a composition for use as a prophylactic in the control of prevention of diseases or infections of the human or animal body caused by pathogens and for use in the relevant fields of application as herein defined, the composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC;

provided that the guanidine component is not imine octadine triacetate.

The QAC, the guanidine component and the use in the relevant fields of application may be as hereinbefore described.

Additionally provided by the invention is use in the manufacture of a medicament to treat, control or prevent diseases or infections of the human or animal body caused by pathogens, and in the manufacture of an antimicrobial

composition for use in the relevant fields of application as herein defined, of a composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC;

provided that the guanidine component is not imine octadine triacetate.

The QAC, the guanidine component and the use in the relevant fields of application may be as hereinbefore described.

The invention will now be described by way of the following non-limiting, illustrative examples:

Example 1

For each of the fungal species enumerated in the accompanying Tables 1 and 2, a spore suspension was made and diluted to a concentration of 4×10^2 spores/ml. Thereafter, 250 μl of this spore suspension (equivalent to 100 spores) was removed as a control, added to a QAC inactivator and poured into a petri dish. 20 ml of liquid MEA (45°c) was added and mixed. 5ml aliquots of the spore suspension were added to 5 ml aliquots of dilutions (the dilutions being adjusted depending on final dilutions of solutions A to C required for each test) of each of the solutions A to C. For the tests involving 1:1000 dilutions of the test solutions, the 5ml aliquots of the solutions A to C were 1:500 dilutions.

Solution A = 12% aqueous solution of Didecyl dimethyl ammonium chloride.

Solution B = 1,5% aqueous solution of bis(8-guanidino-octyl) amine acetate.

Solution C = Solution A + Solution B.

After the time periods indicated in Tables 1 and 2 for each of the tests, 0,5 ml was removed and added to 0,5 ml sterile QAC inactivator and mixed. The inactivated spore suspension (representing 100 spores) was poured into a petri dish and 20 ml liquid MEA (45°C) was added to the suspension and mixed with it. The petri dishes were incubated and scored after 6, 12 or 24 hours. Tables 1 and 2 illustrate the results of tests involving two different fungal species. The

synergistic effect of the antimicrobial composition is apparent in the results for Solution C, as compared with those for Solutions A and B.

TABLE 1

Maximum counts (average from 6 replications) of *Aspergillus niger* ATCC90196 after exposure to 1:1000 dilutions of test Solutions A, B and C for varying time intervals.				
	Control	1 minute	5 minutes	20 minutes
Solution A	38.3	25 (65%)	13.7 (36%)	1,7 (4,5%)
Solution B	60	60 (100%)	50 (83%)	45 (75%)
Solution C	38	22,4 (59%)	7,7 (20%)	0,2 (0,5%)

TABLE 2

Maximum counts (average from 6 replications) of *Penicillium* sp. after exposure to 1:1000 dilutions of test solutions A, B and C for varying time intervals.			
	Control	1 minute	5 minutes
Solution A	90,5	26,5 (29%)	2.85 (3,2%)
Solution B	90,5	45 (50%)	40 (44%)
Solution C	90,7	7,7 (8,5%)	0,3 (0,3%)

Example 2

Six solutions (solutions A to F below) were diluted to 1:1000 in sterile, deionised water. Filter paper disks were soaked in the resulting diluted solutions and placed on PDA plates. These plates were inoculated with dry conidia of *Aspergillus niger* in a spore-settling tower. Diameters of inhibition zones around the filter paper disks were measured perpendicularly at various day intervals after inoculation. Mean inhibition zone diameters are tabulated against time in the accompanying Table 3, indicating the antimicrobial effectiveness of the solutions A to F.

Solution A = 12% aqueous solution of Didecyl dimethyl ammonium chloride; Solution B = 1,5% aqueous solution of bis (8-guanidino-octyl) amine acetate; Solution C = Solution A + Solution B; Solution D = Solution E + Solution F; Solution E = 6,75% aqueous solution of bis (8-guanidino-octyl) amine acetate; Solution F = 6,75% aqueous solution of Didecyl dimethyl ammonium chloride.

TABLE 3

Percentage inhibition of *Aspergillus niger* around 13 mm filter paper disks soaked in dilutions of Solutions A to F after 4, 7 and 14 days incubation at 22°C.			
Dilution 1:1000 of:	**4 days**	**7 days**	**14 days**
Solution A	0%	0%	0%
Solution B	2,5%	2,5%	1,5%
Solution C	5,5%	5,5%	4%
Solution D	10,5%	10,5%	8,5%
Solution E	6%	6%	4,5%
Solution F	0%	0%	0%
Control	0%	0%	0%

Example 3

The following groups of dilutions of the chemical species indicated in each case were prepared using deionized water adjusted to pH 9 using sodium hydroxide:

Group 1 = Didecyl dimethyl ammonium chloride:

800 ppm, 400 ppm, 200 ppm, 150 ppm, 100 ppm, 50 ppm, 25 ppm, 10 ppm, 5 ppm, 2,5 ppm, etc.

Group 2 = bis (8-guanidino-octyl) amine acetate:

80 ppm, 40 ppm, 20 ppm, 15 ppm, 10 ppm, 5 ppm, 2,5 ppm, 1 ppm, 0,5 ppm, 0,25 ppm, etc.

Group 3 = Combinations of dilutions from Groups 1 + 2:

800 ppm (didecyl) + 80 ppm (guanidino), 400 ppm (didecyl) + 40 ppm (guanidino), etc.

Group 4 = Control (containing no active ingredient)

5 ml of each of the dilutions was inoculated with 5 ml of a solution containing 10^6 cfu/ml of *Escherichia coli*. The resulting solutions were then well mixed, capped and held at ambient room temperature. After 1 hour and after 24 hours, 500 $\mu\ell$ of each of the solutions was removed and added to 500 $\mu\ell$ sterile QAC inactivator and mixed. 100 $\mu\ell$ of the resulting inactivated bacterial suspension from each solution was added to 9,9 ml of sterile distilled water and the resulting dilution was mixed. 250 $\mu\ell$ of this diluted bacterial suspension was pipetted into a petri dish and 20 ml nutrient agar was added to it and mixed with it. The petri dishes were incubated and scored after 24 hours for growth. Similar procedures were followed with 10^7 cfu/ml of *Pseudomonas auriginosa* and 10^7 cfu/ml of *Staphylococcus aureus*. Results of the scoring are tabulated in the accompanying Table 4.

TABLE 4

Minimum concentration needed for 99,9% kill rate								
	Control		Didecyl		Guanidino		Combination	
Microbe	1 hour	24 hrs	1 hour	24 hrs	1 hour	24 hrs	1 hour	24 hrs
E. coli	$>10^6$ cfu's	$>10^6$ cfu's	150 ppm	40 ppm	80 ppm	8 ppm	50 ppm + 5 ppm	5 ppm + 0,5 ppm
Pseudomonas auriginosa	$>10^7$ cfu's	$>10^7$ cfu's	300 ppm	120 ppm	320 ppm	40 ppm	200 ppm + 20 ppm	25 ppm + 2,5 ppm
Staphylococcus aureus	$>10^7$ cfu's	$>10^7$ cfu's	0,5 ppm	0,5 ppm	1 ppm	1 ppm	0,25 ppm + 0,026 ppm	0.125 ppm + 0,013 ppm

Example 4

Tests were conducted *in vitro* and *in ovo* against a virus count of TCID > 1 000 000. The virus and the active ingredients were mixed with skimmed milk and $CaCo_3$ to form a solution containing 1% skimmed milk, 300 ppm $CaCo_3$, the

virus and 1% dilution of Product A. The virus was exposed to this solution for 30 minutes whereafter viral survival counts were taken to demonstrate the efficacy of the combined active ingredients.

The following active ingredients were mixed together in distilled water to form an aqueous solution which was labelled Product A:

Product A comprised 86,5% water + 12% aqueous solution of didecyl-dimethylammonium chloride + a 1,5% aqueous solution of guanidino compounds, synthesised from octamethylene diamine (comprising 20% guanidinised diamines and 80% guanidinised triamines and higher oligomers with a guanidinisation grade of 85%).

The results of the tests are set out in Table 5 below.

TABLE 5

Results of Virus kill rate when exposed to a 1% dilution of Product A:	
Feline calicivirus	100% kill rate
Canine parvovirus	100% kill rate
Newcastle Disease virus	100% kill rate
Infectious Bursal Disease virus	100% kill rate
Avian pox virus	100% kill rate

Example 5

An example of a topical composition, broadly in accordance with the invention, is a topical cream formulation as set out below.

Cream 5% formulation (w/w)

(C_{12} - C_{16}) Alkyl-benzyl ammonium chloride	40 parts
Guanidinised Triamines (synthesised from Octamethylene Diamine)	8 parts
Emulsifying wax B.P.	92 parts

White soft paraffin	150 parts
Liquid paraffin	60 parts
Chlorocreosol	1 part
Purified water	649 parts

Example 6

An example of a composition for liquid oral administration, broadly in accordance with the invention, is:

Solution 12% formulation (w/w)

Didecyl dimethyl ammonium chloride	20 parts
25% Guanidinised diamines (synthesised from Octamethylene Diamine)	1 part
75% Guanidinised triamines (synthesised from Octamethylene Diamine)	3 parts
Nonionic surfactant (NP 9)	4 parts
Water	172 parts

Example 7

For each of the fungal species enumerated in the accompanying Tables 6 to 8, a spore suspension was made and diluted to a concentration of 4 X 10^2 spores/ml. Thereafter, 250 μl of this spore suspension (equivalent to 100 spores) was removed as a control, added to a QAC inactivator and poured into a petri dish. 20 ml of liquid MEA (45°c) was added and mixed. 5ml aliquots of the spore suspension were added to 5 ml aliquots of dilutions (the dilutions being adjusted depending on final dilutions of solutions A to C required for each test) of each of the solutions A to C. For the tests involving 1:1000 dilutions of the test solutions, the 5ml aliquots of the solutions A to C were 1:500 dilutions.

Solution A = 12% aqueous solution of Didecyl dimethyl ammonium chloride.

Solution B = 1,5% aqueous solution of bis(8-guanidino-octyl) amine acetate.

Solution C = Solution A + Solution B.

After the time periods indicated in Tables 6 to 8 for each of the tests, 0,5 ml was removed and added to 0,5 ml sterile QAC inactivator and mixed. The inactivated spore suspension (representing 100 spores) was poured into a petri dish and 20 ml liquid MEA (45°C) was added to the suspension and mixed with it. The petri dishes were incubated and scored after 6, 12 or 24 hours. Tables 6 to 8 illustrate the results of tests involving five different fungal species. The synergistic effect

of the antimicrobial composition is apparent in the results for Solution C, as compared with those for Solutions A and B.

TABLE 6

Maximum counts (average from 3 replications) of *Phanerochaete chrysosporium* after exposure to 1:1000 dilutions of test solutions A, B and C for varying time intervals ("+" = 30 colonies).		
	Control	1 minute
Solution A	+ + +	+
Solution B	+ + +	+ + +
Solution C	+ + +	1/3 +

TABLE 7

Maximum counts of *Alternaria alternata* after exposure to 1:2000 dilutions (for 5 and 10 minutes) and 1:4000 dilutions (for 20 minutes) of test solutions A, B and C for varying time intervals.				
	Control	5 minutes (500 ppm)	10 minutes (500 ppm)	20 minutes (250 ppm)
Solution A	>200	116 (58%)	22 (11%)	6 (3%)
Solution B	>200	>200 (100%)	>200 (100%)	>200(100%)
Solution C	>200	58 (29%)	4 (2%)	2 (1%)

TABLE 8

Maximum counts (average from 3 replications) of *Trichoderma harzianum* after exposure for 5 minutes to various dilutions of test solutions A, B and C.				
	Control	250 ppm	100 ppm	50 ppm
Solution A	32	6 (19%)	5 (16%)	3 (9,5%)
Solution B	32	32 (100%)	32 (100%)	32 (100%)
Solution C	32	0 (0%)	1 (3%)	2 (6,5%)

Example 8

Six solutions (solutions A to F below) were diluted to 1:1000 in sterile, deionised water. Filter paper disks were soaked in the resulting diluted solutions and placed on PDA plates. These plates were inoculated with dry conidia of *Botrytis cinerea* in a spore-settling tower. Diameters of inhibition zones around the filter paper

disks were measured perpendicularly at various day intervals after inoculation. Mean inhibition zone diameters are tabulated against time in the accompanying Tables 9, indicating the antimicrobial effectiveness of the solutions A to F.

Solution A = 12% aqueous solution of Didecyl dimethyl ammonium chloride; Solution B = 1,5% aqueous solution of bis (8-guanidino-octyl) amine acetate; Solution C = Solution A + Solution B; Solution D = Solution E + Solution F; Solution E = 6,75% aqueous solution of bis (8-guanidino-octyl) amine acetate; Solution F = 6,75% aqueous solution of Didecyl dimethyl ammonium chloride.

TABLE 9

Percentage inhibition of *Botrytis cinerea* around 13 mm filter paper disks soaked in dilutions of Solutions A to F and Control after 4,7 and 14 days incubation at 22°C.			
Dilution 1:1000 of:	**4 days**	**7 days**	**14 days**
Solution A	3,5%	0%	0%
Solution B	1,5%	1%	0%
Solution C	6,5%	5,5%	3%
Solution D	11,5%	9,5%	9,5%
Solution E	5,5%	2%	0,5%
Solution F	2,1%	0%	0%
Control	0%	0%	0%

Example 9

This example illustrates *in vivo* use of the antimicrobial composition as compared with *in vivo* use of the individual active ingredients to combat fungi which affect oranges and bananas after harvesting. Different preparations containing 3 solutions (solutions A to C below) were tested and compared in an irradicant dip-test against *Gloeosporium musarum*. The following method was adopted:

10 slices of banana peel each having a diameter of 10 mm were submerged in aqueous suspensions containing 1000, 3000 and 10 000 ppm of the test solutions, 2 hours after grafting with a *Gloeosporium musarum* spore suspension of 10^6 cells/ml. The slices were put in five separate plastic "REPLIDISHes" (trade name) at random, in which the relative humidity was kept high with the aid of

moist filter paper for 1 week. "REPLIDISH" is a trade name for a petri dish having dimensions of 10 cm x 10 cm, and which is subdivided into 35 squares sealed off from one another by means of vertical partitions of synthetic material.

The accompanying Table 10 tabulates % infection after 1 week following treatment with the dilute aqueous suspensions.

Solution A = 12% aqueous solution of Didecyl dimethyl ammonium chloride;
Solution B = 1,5% aqueous solution of bis(8-guanidino-octyl) amine acetate;
Solution C = Solution A + Solution B.

TABLE 10

% infection caused by *Gloeosporium musarum* on bananas, after treatment with Solutions A to C.				
	Solution A	Solution B	Solution C	Control
1000 ppm	51,1	81	22	89,6
3000 ppm	25,8	43,4	9,2	89,6
10 000 ppm	18,3	29,5	4	89,6

Example 10

This example illustrates the suppression of fungi (specifically *Botrytis cinerea*) on tomato plants, after disinfection using 3 solutions:

Solution A = 12% aqueous solution of Didecyl dimethyl ammonium chloride; Solution B = 1,5% aqueous solution of bis (8-guanidino-octyl) amine acetate; Solution C = Solution A + Solution B.

Tomato plants (variety: "Outdoor Girl") in the two-leaves-stage and approximately 3 month old, were inoculated with a suspension of 5 X 10^3 spores/ml in sufficient quantities to wet the plants. Once the plants were dry, they were sprayed with the test solutions (solutions A to C) in a quantity of 2 ml per plant at a 1000 ppm concentration of each solution.

The plants were then placed in humidifier cabinets for 48 hours at a temperature of 18.3°C and a relative humidity of 100%. Subsequently they were removed and kept in a hothouse for 3 to 4 days for assessment. The assessment

was performed visually and qualifications were assigned for different degrees of disease of the plants as follows:

Qualification	Degree of Disease
0	60 to 100%
1	25 to 60%
2	5 to 25%
3	1 to 5%
4	no disease

The results obtained are represented in Table 11.

TABLE 11

% Efficacy in disinfection of tomato plant surfaces inoculated with *Botrytis cinerea*.			
Control	Solution A	Solution B	Solution C
0	1	1	3

Example 11

The antimicrobial activity of the composition of the invention, and the individual active ingredients making up the composition, were tested *in vivo*, against microbes that cause rot in prepacked vegetable produce packaged in polythene or similar containers, e.g. polythene bags. The microbes were not specifically identified but may have included fungi and/or bacteria.

Vegetables prepared for retail (whole, cut, pre-washed and/or otherwise processed) were dipped in aqueous solutions containing 1000 ppm of each of the 3 solutions tested.

Solution A = 12% aqueous solution of Didecyl dimethyl ammonium chloride; Solution B = 1,5% aqueous solution of bis (8-guanidino-octyl) amine acetate; Solution C = Solution A + Solution B.

A control treatment whereby vegetables were submerged in water only was used in all tests. The water used was that normally used for the washing of produce on a commercial scale. For each test, 50 litres of the relevant solution

was prepared in a large rigid polythene container. Prepared vegetables were placed into polythene mesh nets and immersed in a solution for a particular treatment for 3 minutes, after which they were taken out and left to dry on trays. The vegetables of the 4 separate treatments were packaged in 4 replicas of polythene bags or similar containers used for packaging of vegetables for retail. The quantity of vegetables per pack was similar to the quantity per pack of vegetables which are prepared for retail. The packs were arranged in randomised block designs, each design comprising 10 replicas. The packs were stored at 22°C to encourage rots to develop on the vegetables. Table 12 tabulates percentage unsaleable produce after storage.

TABLE 12

Percentage unsaleable produce after treatment with 1000 ppm of each solution.				
	Solution A	Solution B	Solution C	Control
Celery	24%	31%	6,1%	45,3%
Leeks	13,5%	20,4%	7,5%	24%
Lettuce	11,1%	7,5%	2,5%	10,2%
Cabbage	5,3%	8,1%	2,1%	12,5%

Example 12

This example illustrates application of the antimicrobial composition and the individual active ingredients of the composition, to extend the life span of cut flowers in vases, through control of microbes such as fungi and bacteria in water in such vases.

Tests were carried out, involving application of the following 3 solutions at a concentration of 1000 ppm:

Solution A = 12% aqueous solution of Didecyl dimethyl ammonium chloride; Solution B = 1,5% aqueous solution of bis (8-guanidino-octyl) amine acetate; Solution C = Solution A + Solution B.

In each of the tests, freshly cut flowers were treated as follows:

The stem of each flower was cut off approximately 2.5 cm from the base of the flower. The stems of the flowers were individually inserted into 100 ml measuring cylinders, each containing 100 ml of the test solutions. A 5 ml aliquot containing 10^3 cells/ml of a mixture of bacteria (*E.coli and Pseudomonas* sp.) and 10^2 spores/ml of a fungus (*Fuserium* sp.) was used to inoculate each test solution. Cotton wool was packed around the neck of each cylinder in order to reduce evaporation. In all tests, deionised water was used instead of tap water. 30 replica cylinders were used per solution tested.

Criteria used to determine the vase life of the flowers varied depending on the flower type. Control carnations curled upwards becoming "sleepy", and finally shrivelled, whereas flowers that were treated with the test solutions hardly ever looked as though they became "sleepy", although they did eventually show signs of scorching of the petals. Assessment took place when shrivelling or scorch first appeared. Table 13 tabulates the effect of the dilute test solutions and Control on the vase life of carnations.

TABLE 13

Vase life of Carnations (variety: "White sim") treated with different test solutions and Control.			
Control	Solution A	Solution B	Solution C
5 days	9 days	6 days	13 days

Having thus exemplified the invention, advantages of the compositions as exemplified are considered.

An advantage of the pharmaceutical composition as herein described, is that the combination of the two active ingredients has an increased potency and broadening effect on the overall efficacy of the ingredients when used together against pathogens such as fungi, bacteria and viruses, as opposed to when they are applied individually. There is therefore both an economical and practical advantage to the use of the combination in combating pathogens.

It is an advantage of the antimicrobial composition as herein described that its effect in the inhibition of microbial growth in the relevant fields of application is synergistic rather than merely additive of the individual effects of the respective active ingredients.

This synergy was not expected and is manifested in a surprising lengthening and broadening of the antimicrobial spectrum that cannot only be ascribed to an additive effect of combining the active ingredients.

A number of advantages emanate from this synergy. For example, this synergy permits a reduction in quantities of the active ingredients needed for effective usage of the antimicrobial composition. There is a decrease in potential negative impacts on the environment, a reduction in costs, a reduction in residue levels on target plants and in water systems, a reduction in risks of phytotoxicity to plants, an increase in the potential range of plants which may benefit by treatment with the composition, an increase in the antimicrobial efficacy and spectrum associated with the composition and, consequently, a decrease in the

frequency and range of antimicrobial treatments required for a particular application.

CLAIMS:

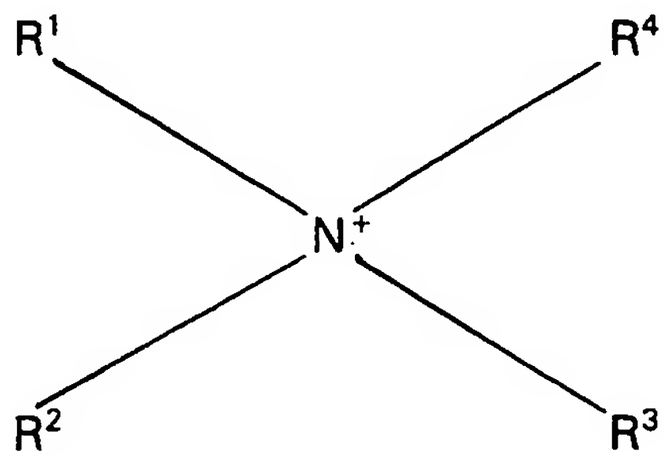
1. A substance or composition for use in a method of treatment of a human or animal body by therapy, the substance or composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC;

said method comprising administering an effective amount of said substance or composition to said human or animal body.

2. A substance or composition as claimed in Claim 1, in which the QAC is represented by the general formula (I)



.....(I)

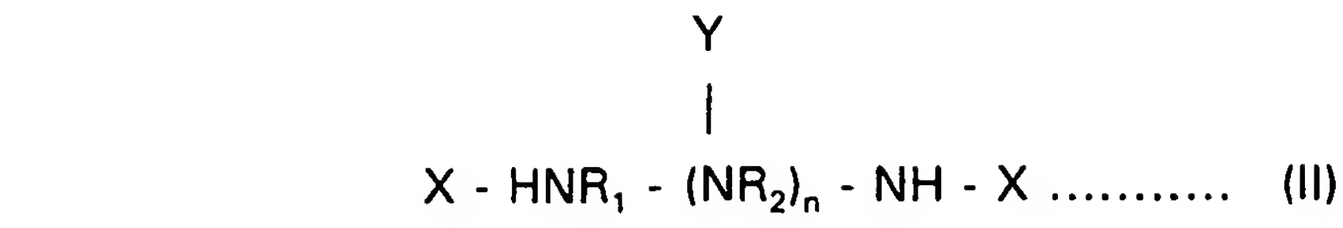
wherein:

at least one of R_1, R_2, R_3 and R_4 is an acyclic group having 6 to 24 carbon atoms;

when any two of R_1, R_2, R_3 and R_4 each is an acyclic group having 6 to 24 carbon atoms, then the remainder of R_1, R_2, R_3 and R_4 are each independently selected from alkyl and hydroxyalkyl groups having 1 to 4 carbon atoms, and a benzyl group; and may together with the nitrogen atom form a piperidinyl or morpholinyl group; and

X^- is chloride or any other pharmaceutically acceptable anion.

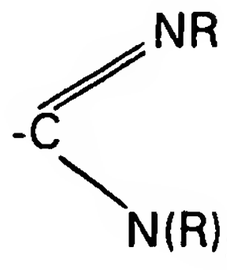
3. A substance or composition as claimed in Claim 1 or Claim 2, in which the guanidine component includes guanidine compounds having a general formula (II)



$$X - HNR_1 - (NR_2)_n - NH - X \quad \text{.....} \quad (II)$$

wherein:

X and Y are each hydrogen or a carboxamidine group having a general formula (III)



.....(III)

wherein R is H or an alkyl group having 1-4 carbon atoms, with the proviso that at least one of X and Y must be a carboxamidine group of formula (III) as defined above;

R_1 and R_2 are alike or independently different aliphatic groups selected from groups having 3-14 carbon atoms, preferably alkyl groups having 6-12 carbon atoms including those selected from the group consisting of hexyl, heptyl, octyl, nonyl, decyl, and dodecyl, most preferably alkyl groups having 6-9 carbon atoms; or cycloalkyl groups selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and

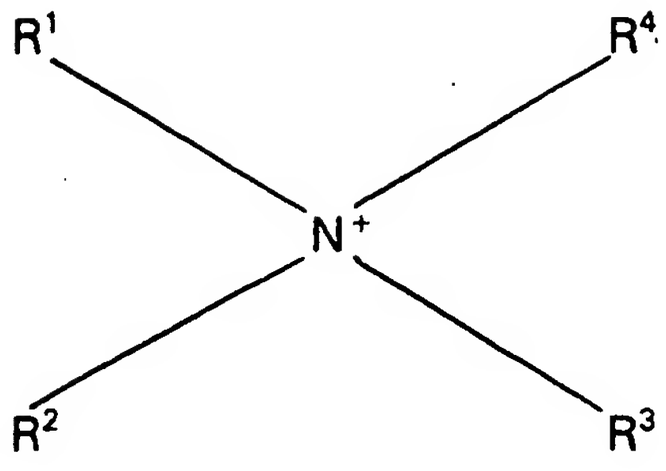
n is 0 to 6, preferably 0 to 4; provided that for values of $n > 1$, R_2 may differ for each value of n.

4. Use in the manufacture of a medicament to treat, control or prevent diseases or infections of the human or animal body caused by pathogens, of a composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC.

5. Use as claimed in Claim 4, in which the QAC is represented by the general formula (I)



.....(I)

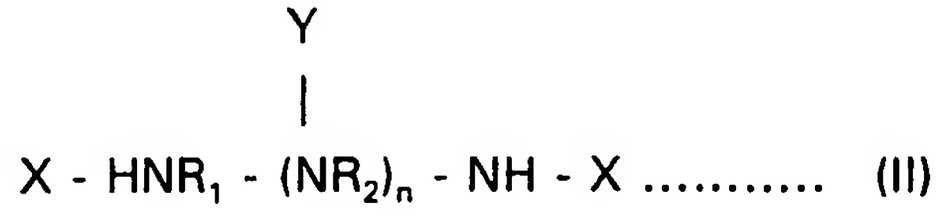
wherein:

at least one of R_1, R_2, R_3 and R_4 is an acyclic group having 6 to 24 carbon atoms;

when any two of R_1, R_2, R_3 and R_4 each is an acyclic group having 6 to 24 carbon atoms, then the remainder of R_1, R_2, R_3 and R_4 are each independently selected from alkyl and hydroxyalkyl groups having 1 to 4 carbon atoms, and a benzyl group; and may together with the nitrogen atom form a piperidinyl or morpholinyl group; and

X^- is chloride or any other pharmaceutically acceptable anion.

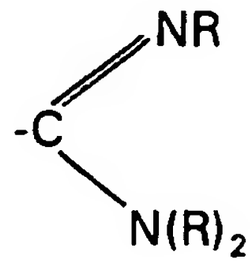
6. Use as claimed in Claim 4 or Claim 5, in which the guanidine component includes guanidine compounds having a general formula (II)



$$X - HNR_1 - (NR_2)_n - NH - X \quad \text{.....} \quad (II)$$

wherein:

X and Y are each hydrogen or a carboxamidine group having a general formula (III)



.....(III)

wherein R is H or an alkyl group having 1-4 carbon atoms, with the proviso that at least one of X and Y must be a carboxamidine group of formula (III) as defined above;

R_1 and R_2 are alike or independently different aliphatic groups selected from groups having 3-14 carbon atoms, preferably alkyl groups having 6-12 carbon

atoms including those selected from the group consisting of hexyl, heptyl, octyl, nonyl, decyl, and dodecyl, most preferably alkyl groups having 6-9 carbon atoms; or cycloalkyl groups selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and

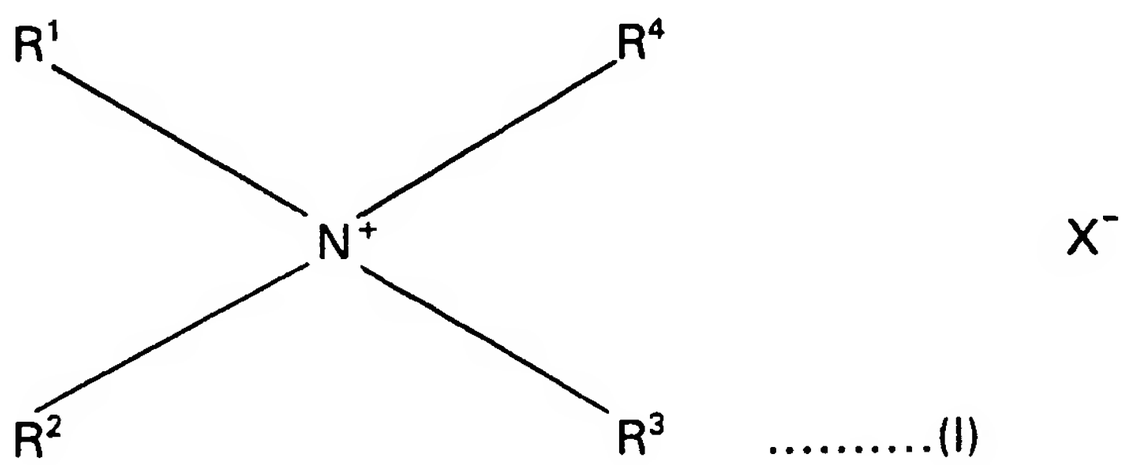
n is 0 to 6, preferably 0 to 4; provided that for values of $n>1$, R_2 may differ for each value of n.

7. A method of treatment or prophylaxis of diseases or infections of a human or animal body caused by pathogens, the method including the steps of administering to an afflicted human or animal body a composition which includes, in combination as active ingredients,

a guanidine component; and

at least one QAC.

8. A method as claimed in Claim 7, in which the QAC is represented by the general formula (I)



.....(I)

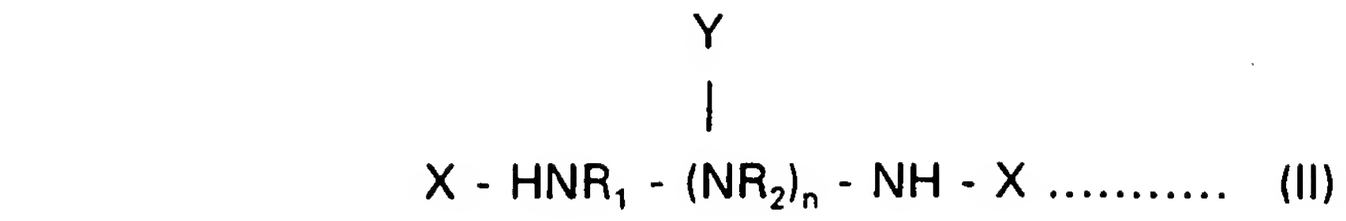
wherein:

at least one of R_1, R_2, R_3 and R_4 is an acyclic group having 6 to 24 carbon atoms;

when any two of R_1, R_2, R_3 and R_4 each is an acyclic group having 6 to 24 carbon atoms, then the remainder of R_1, R_2, R_3 and R_4 are each independently selected from alkyl and hydroxyalkyl groups having 1 to 4 carbon atoms, and a benzyl group; and may together with the nitrogen atom form a piperidinyl or morpholinyl group; and

X^- is chloride or any other pharmaceutically acceptable anion.

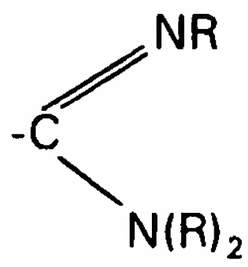
9. A method as claimed in Claim 7 or Claim 8, in which the guanidine component includes guanidine compounds having a general formula (II)



$$X - HNR_1 - (NR_2)_n - NH - X \quad \text{.....} \quad (II)$$

wherein:

X and Y are each hydrogen or a carboxamidine group having a general formula (III)



.....(III)

wherein R is H or an alkyl group having 1-4 carbon atoms, with the proviso that at least one of X and Y must be a carboxamidine group of formula (III) as defined above;

R_1 and R_2 are alike or independently different aliphatic groups selected from groups having 3-14 carbon atoms, preferably alkyl groups having 6-12 carbon atoms including those selected from the group consisting of hexyl, heptyl, octyl, nonyl, decyl, and dodecyl, most preferably alkyl groups having 6-9 carbon atoms; or cycloalkyl groups selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and

n is 0 to 6, preferably 0 to 4; provided that for values of $n>1$, R_2 may differ for each value of n.

10. A composition for use as a prophylactic in the control or prevention of diseases or infections of the human or animal body caused by pathogens, the composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC.

11. A composition as claimed in Claim 10, in which the QAC is represented by the general formula (I)

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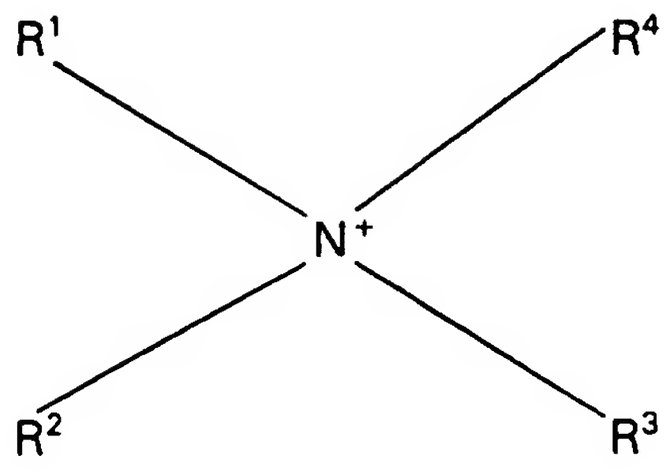


.....(I)

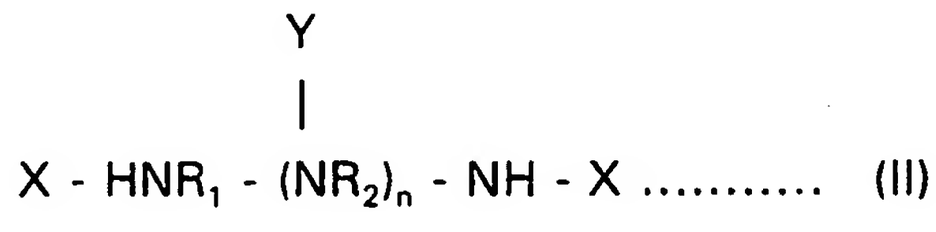
wherein:

at least one of R_1, R_2, R_3 and R_4 is an acyclic group having 6 to 24 carbon atoms;

when any two of R_1, R_2, R_3 and R_4 each is an acyclic group having 6 to 24 carbon atoms, then the remainder of R_1, R_2, R_3 and R_4 are each independently selected from alkyl and hydroxyalkyl groups having 1 to 4 carbon atoms, and a benzyl group; and may together with the nitrogen atom form a piperidinyl or morpholinyl group; and

X^- is chloride or any other pharmaceutically acceptable anion.

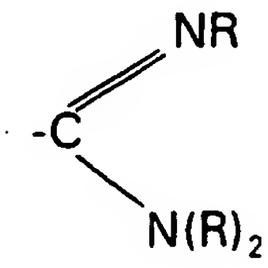
12. A composition as claimed in Claim 10 or Claim 11, in which the guanidine component includes guanidine compounds having a general formula (II)



$$X - HNR_1 - (NR_2)_n - NH - X \quad \text{.....} \quad (II)$$

wherein:

X and Y are each hydrogen or a carboxamidine group having a general formula (III)



.....(III)

wherein R is H or an alkyl group having 1-4 carbon atoms, with the proviso that at least one of X and Y must be a carboxamidine group of formula (III) as defined above;

R_1 and R_2 are alike or independently different aliphatic groups selected from groups having 3-14 carbon atoms, preferably alkyl groups having 6-12 carbon atoms including those selected from the group consisting of hexyl, heptyl, octyl, nonyl, decyl, and dodecyl, most preferably alkyl groups having 6-9 carbon atoms; or cycloalkyl groups selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and

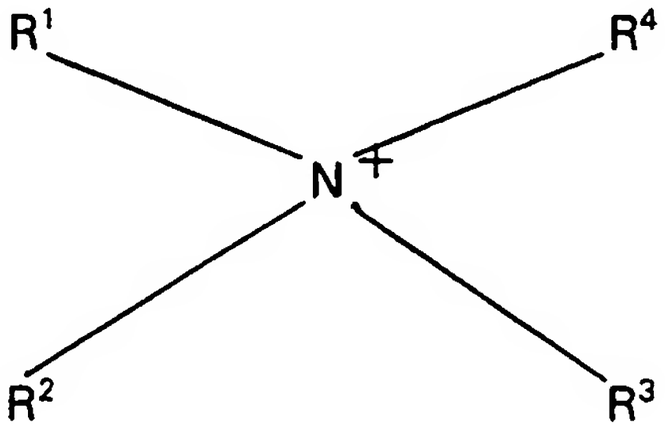
n is 0 to 6, preferably 0 to 4; provided that for values of $n>1$, R_2 may differ for each value of n.

13. A disinfectant composition which includes, in combination as active ingredients,

a guanidine component; and

at least one QAC.

14. A disinfectant composition as claimed in Claim 13, in which the QAC has a general formula (IA)



.....(IA)

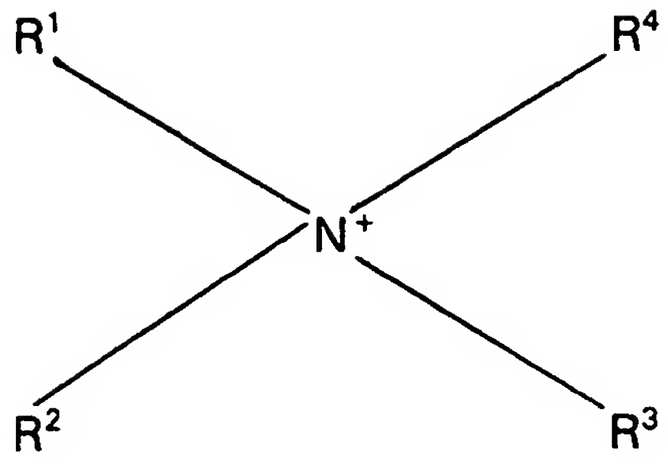
wherein:

R^1 and R^4 are the same or different and each is independently selected from the group consisting of C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{20} aryl, C_4-C_{20} alkaryl, C_4-C_{20} aralkyl and C_5-C_{20} alkaraIkyl;

R^2 and R^3 are the same or different and each is independently C_1-C_6 alkyl; and

X^- is an anion.

15. A disinfectant composition as claimed in Claim 13, in which the QAC is represented by the general formula (I)



.....(I)

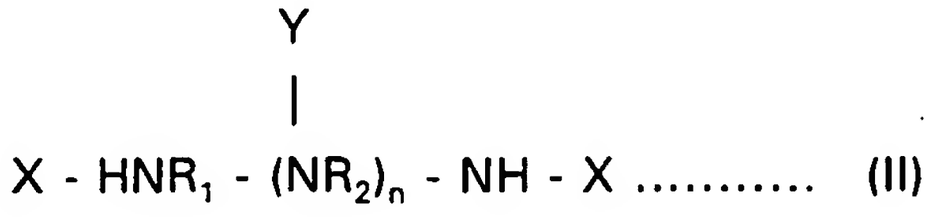
wherein:

at least one of R_1, R_2, R_3 and R_4 is an acyclic group having 6 to 24 carbon atoms;

when any two of R_1, R_2, R_3 and R_4 each is an acyclic group having 6 to 24 carbon atoms, then the remainder of R_1, R_2, R_3 and R_4 are each independently selected from alkyl and hydroxyalkyl groups having 1 to 4 carbon atoms, and a benzyl group; and may together with the nitrogen atom form a piperidinyl or morpholinyl group; and

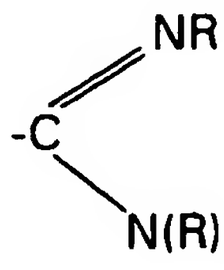
X^- is chloride or any other pharmaceutically acceptable anion.

16. A disinfectant composition as claimed in any one of Claims 13 to 15 inclusive, in which the guanidine component includes guanidine compounds having a general formula (II)



wherein:

X and Y are each hydrogen or a carboxamidine group having a general formula (III)



.....(III)

wherein R is H or an alkyl group having 1-4 carbon atoms, with the proviso that at least one of X and Y must be a carboxamidine group of formula (III) as defined above;

R_1 and R_2 are alike or independently different aliphatic groups selected from groups having 3-14 carbon atoms, preferably alkyl groups having 6-12 carbon atoms including those selected from the group consisting of hexyl, heptyl, octyl, nonyl, decyl, and dodecyl, most preferably alkyl groups having 6-9 carbon atoms; or cycloalkyl groups selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and

n is 0 to 6, preferably 0 to 4; provided that for values of $n > 1$, R_2 may differ for each value of n.

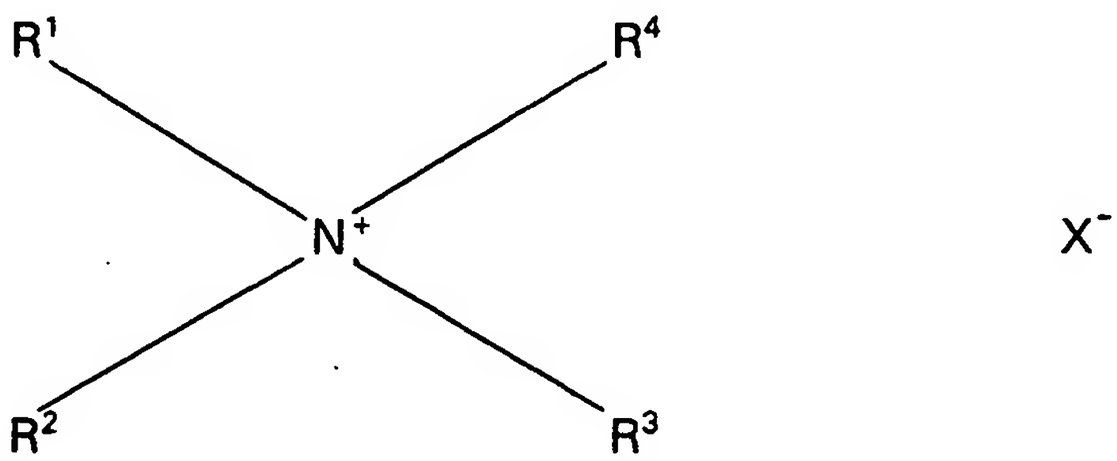
17. A pharmaceutical composition for use in the treatment or prophylaxis of diseases or infections of a human or animal body caused by pathogens, the pharmaceutical composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC;

the pharmaceutical composition further including at least one ingredient selected from the group consisting of carriers, excipients, diluents and adjuvants.

18. A pharmaceutical composition as claimed in Claim 17, in which the QAC is represented by the general formula (I)



.....(I)

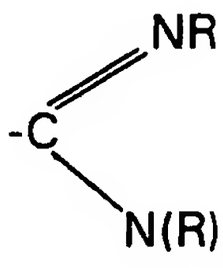
wherein:

at least one of R_1, R_2, R_3 and R_4 is an acyclic group having 6 to 24 carbon atoms;

when any two of R_1, R_2, R_3 and R_4 each is an acyclic group having 6 to 24 carbon atoms, then the remainder of R_1, R_2, R_3 and R_4 are each independently selected from alkyl and hydroxyalkyl groups having 1 to 4 carbon atoms, and a benzyl group; and may together with the nitrogen atom form a piperidinyl or morpholinyl group; and

X^- is chloride or any other pharmaceutically acceptable anion.

19. A pharmaceutical composition as claimed in Claim 17 or Claim 18, in which the guanidine component includes guanidine compounds having a general formula (II)



$$X - HNR_1 - (NR_2)_n - NH - X \quad \text{.....} \quad (II)$$

wherein:

X and Y are each hydrogen or a carboxamidine group having a general formula (III)

.....(III)

wherein R is H or an alkyl group having 1-4 carbon atoms, with the proviso that at least one of X and Y must be a carboxamidine group of formula (III) as defined above;

R_1 and R_2 are alike or independently different aliphatic groups selected from groups having 3-14 carbon atoms, preferably alkyl groups having 6-12 carbon atoms including those selected from the group consisting of hexyl, heptyl, octyl, nonyl, decyl, and dodecyl, most preferably alkyl groups having 6-9 carbon atoms; or cycloalkyl groups selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and

n is 0 to 6, preferably 0 to 4; provided that for values of $n > 1$, R_2 may differ for each value of n.

20. An antimicrobial composition for use in the relevant fields of application as herein defined, the composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC having a general formula (IA)

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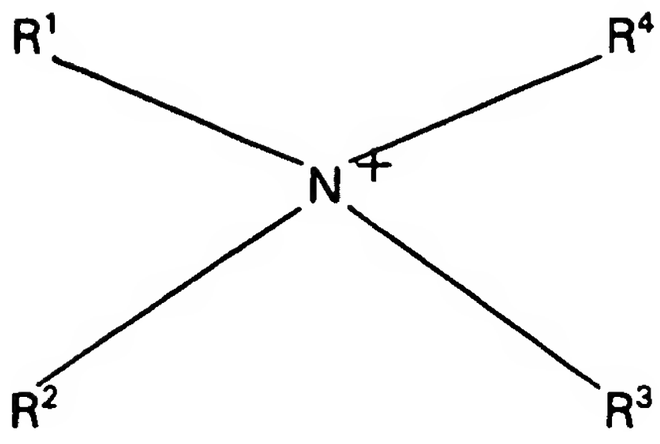


.....(IA)

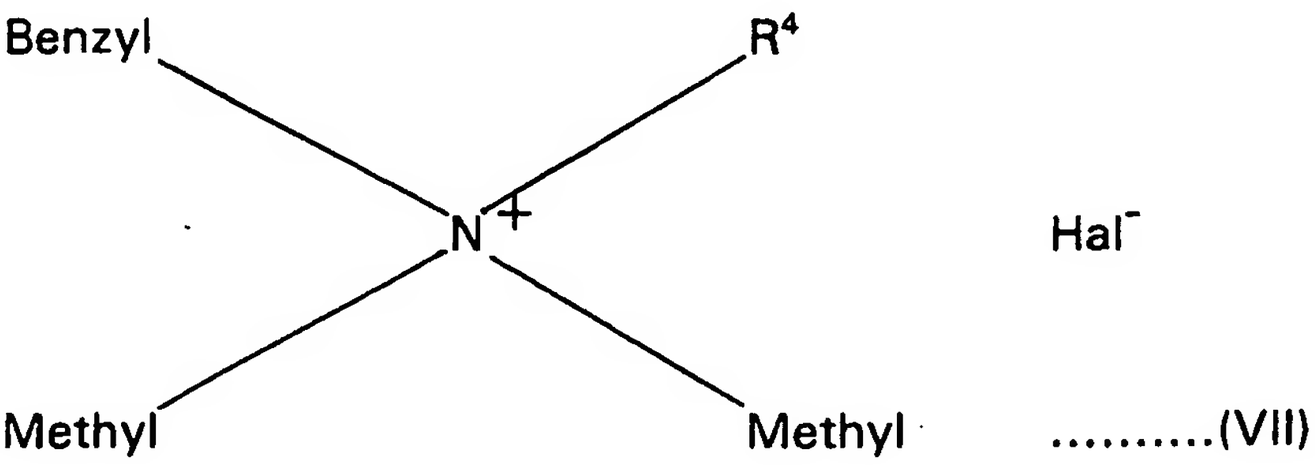
wherein:

R^1 and R^4 are the same or different and each is independently selected from the group consisting of C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{20} aryl, C_4-C_{20} alkaryl, C_4-C_{20} aralkyl and C_5-C_{20} alkaralkyl;

R^2 and R^3 are the same or different and each is independently C_1-C_6 alkyl; and

X^- is an anion.

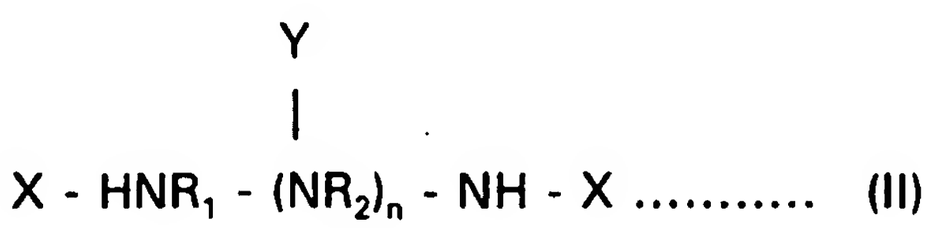
21. An antimicrobial composition as claimed in Claim 20, in which the QAC has a general formula (VII)



.....(VII)

wherein R^4 is alkyl or alkenyl of from 8 to 18, preferably 12 to 18, carbon atoms and "Hal^-" is a chloride or bromide anion.

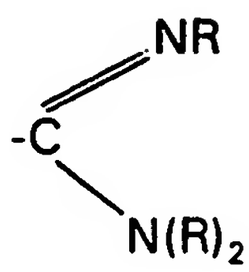
22. An antimicrobial composition as claimed in Claim 20 or Claim 21, in which the guanidine component includes guanidine compounds having a general formula (II)



.....(II)

wherein:

X and Y are each hydrogen or a carboxamidine group having a general formula (III)



.....(III)

wherein R is H or an alkyl group having 1-4 carbon atoms, with the proviso that at least one of X and Y must be a carboxamidine group of formula (III) as defined above;

R_1 and R_2 are alike or independently different aliphatic groups selected from groups having 3-14 carbon atoms, preferably alkyl groups having 6-12 carbon atoms including those selected from the group consisting of hexyl, heptyl, octyl, nonyl, decyl, and dodecyl, most preferably alkyl groups having 6-9 carbon atoms; or cycloalkyl groups selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and

n is 0 to 6, preferably 0 to 4; provided that for values of $n>1$, R_2 may differ for each value of n.

23. An antimicrobial composition as claimed in any one of Claims 20 to 22 inclusive, in which the use of the antimicrobial composition in agriculture, horticulture and floriculture is inhibition and combat of microbes present on growing crops, plants, trees, seeds, flowers, fruits and vegetables, harvested produce (excluding harvested timber), equipment and implement surfaces, packing shed surfaces, or other general agricultural surfaces, or present in or on soils to be used for agricultural purposes, or present in irrigation water, fruit and vegetable dip-tank water or other water used in agriculture.

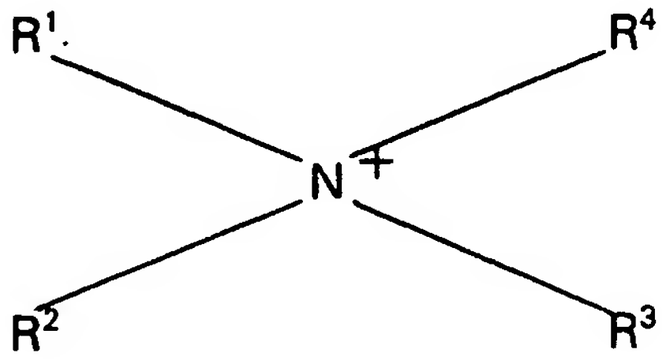
24. An antimicrobial composition as claimed in any one of Claims 20 to 22 inclusive, in which the use of the composition in leather tanning, tobacco and fur processing, paint-, cosmetics-, rope-, plastics-, fuel-, oil- and rubber-manufacture, brewing, canning, bottling, water storage and supply, and shipping is inhibition of microbes growing in aqueous systems employed in these fields.

25. A method of inhibiting growth of microbes in the relevant fields of application as herein defined, which includes the step of contacting said microbes

with a microbicidally effective amount of an antimicrobial composition, the antimicrobial composition including, in combination as active ingredients,

a guanidine component; and

at least one QAC having a general formula (IA)



.....(IA)

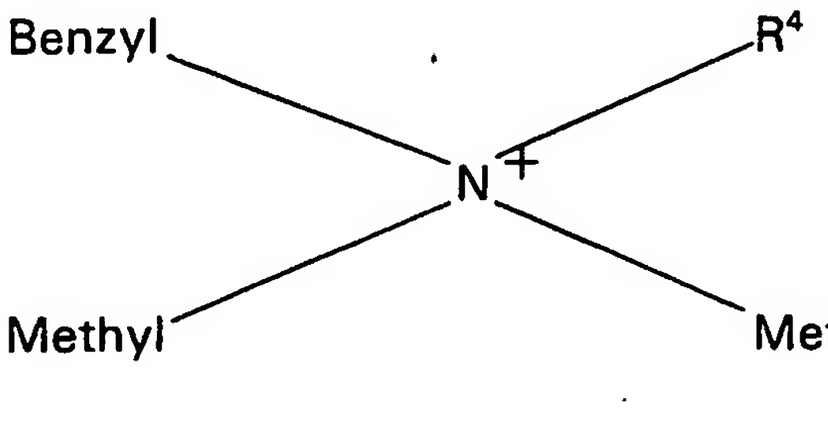
wherein:

R^1 and R^4 are the same or different and each is independently selected from the group consisting of C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{20} aryl, C_4-C_{20} alkaryl, C_4-C_{20} aralkyl and C_5-C_{20} alkaralkyl;

R^2 and R^3 are the same or different and each is independently C_1-C_6 alkyl; and

X^- is an anion.

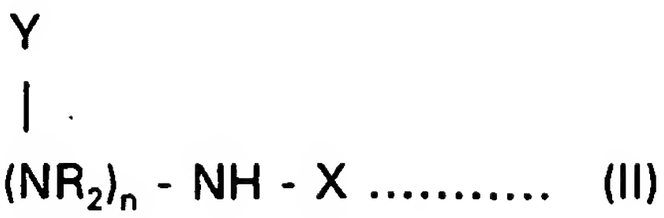
26. A method as claimed in Claim 25, in which the QAC has a general formula (VII)



.....(VII)

wherein R^4 is alkyl or alkenyl of from 8 to 18, preferably 12 to 18, carbon atoms and "Hal^-" is a chloride or bromide anion.

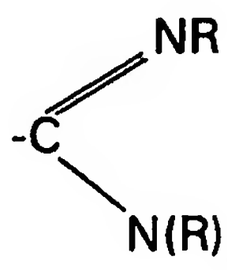
27. A method as claimed in Claim 25 or Claim 26, in which the guanidine component includes guanidine compounds having a general formula (II)



$$X - HNR_1 - (NR_2)_n - NH - X \quad \text{.....} \quad (II)$$

wherein:

X and Y are each hydrogen or a carboxamidine group having a general formula (III)



$$N(R)_2 \quad \text{.....(III)}$$

wherein R is H or an alkyl group having 1-4 carbon atoms, with the proviso that at least one of X and Y must be a carboxamidine group of formula (III) as defined above;

R_1 and R_2 are alike or independently different aliphatic groups selected from groups having 3-14 carbon atoms, preferably alkyl groups having 6-12 carbon atoms including those selected from the group consisting of hexyl, heptyl, octyl, nonyl, decyl, and dodecyl, most preferably alkyl groups having 6-9 carbon atoms; or cycloalkyl groups selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and

n is 0 to 6, preferably 0 to 4; provided that for values of $n > 1$, R_2 may differ for each value of n.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/11761

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/70.28; 510/259, 384, 391, 504; 514/ 20, 556, 642; 534/589, 603; 554/52, 104; 564/230, 237, 241, 242, 281

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN, BIOSIS, MEDLINE, SCISEARCH, MEDLINE CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,000,867 A (HEINUIS-WALTHER et al.) 19 March 1991, see entire document, especially col. 2, lines 40-68.	1-20, 22, 25-27
X	US 5,620,595 A (AUSTIN et al.) 15 April 1997, see col. 8, lines 25-68 and col. 9, lines 1-45.	1-22, 25-27
X	US 5,451,577 A (MORPETH, F.F.) 19 September 1995, see col. 6, lines 40-50 and col. 7, lines 1-35 and lines 65-68.	1-22, 25-27
X	US 5,120,325 A (DOW, JR., J.E.) 09 June 1992, see col. 5, lines 35-65.	1, 2, 4, 5, 7, 8, 10, 11, 13-15, 17, 18, 20, 21, 25, 26

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 AUGUST 1998	15 SEP 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	**Authorized officer** SUSAN HANLEY Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/11761

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,765,984 A (VELLEKOOP et al.) 23 August 1988, see col. 6, lines 62-68, col. 8, lines 1-15.	1-14, 17-20, 22, 25-27
X	US 5,472,972 A (OHKOUCHI et al.) 05 December 1995, see col. 4, lines 55-68 and col. 5, lines 40-50.	1-22, 25-27
X	US 5,256,419 A (ROE et al.) 26 October 1993, see col. 3, lines 35-45.	1-22, 25-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/11761

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6): A61K 31/14; C11D 1/62, 3/84; A61K 38/00; A01N 37/30, 33/12; C07C 229/00, 231/00, 277/00, 211/00; C09C 43/00, 44/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL : 424/70.28; 510/259, 384, 391, 504; 514/ 20, 556, 642; 534/589, 603; 554/52, 104; 564/230, 237, 241, 242, 281

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/11761

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 23 and 24
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.